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REMARKS

Claims Rejection Under 35 U.S.C. §112

Claims 1, 3, 6-9, 11-13 and 16-57 have been rejected under 35 U.S.C. §112, first paragraph. Applicants have amended Claim 1 and 57. Applicants respectfully submit that the term "mediated" is fully supported by the Specification. Specifically, page 14, line 18 states that the "cold shock response of a bacterium are **mediated** by the 5'-untranslated region (5'-UTR) of the mRNA transcripts encoding cold shock inducible proteins." Further support for the phrase "is mediated by a portion of a 5'-UTR of a cold shock inducible gene" can be found on page 5, lines 16-17, page 27, line 23, to page 28, line 5. Applicants further submit that a number of Examples within the Specification, including examples 4-6, and 10-13 illustrate that the 5'-UTR mediates cold shock expression.

Further, Applicants respectfully submit that the Specification clearly demonstrates possession of the 5'-UTR of any of a number of cold shock inducible genes. As is stated in the current office action, the Applicants have clearly described and enabled the 5'-UTR of *cspA*, *cspB*, and *csdA* genes. Not only have Applicants clearly demonstrated the role of the 5'-UTR of *cspA*, *cspB* and *csdA*, but they have also identified that these 5'-UTRs share similar sequence identity. Based on these teachings by the Applicants, one skilled in the art can take the detailed sequence information provided in the Specification to locate the 5'UTRs of any cold shock gene. It is well established in the law that claims are not perforce limited to the embodiments disclosed in the specification. *Amgen Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.*, 65 U.S.P.Q. 2d 1385, 1395 (CAFC 2003); citing e.g., *Rexnord Corp. v. Laitram Corp.*, 60 U.S.P.Q 2d 1851, 1856 (Fed. Cir. 2001) ("an applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention."). In fact,

Enzo Biochem, clarified that not all functional descriptions of genetic material fail as a matter of law to meet the written description requirement; rather the requirement may be satisfied if in the knowledge of the art, the disclosed function is sufficiently correlated to a particularly known structure. See *Enzo Biochem, Inc. v. Gene-Probe, Inc.*, 63 U.S.P.Q. 2d 1609, 1613 (Fed. Cir. 2003). Applicants respectfully submit that not only have the Applicants described the particular function of the claimed genetic material, but also have identified three exemplary genes and their UTRs, which are clearly correlated to the particular function, namely mediation of cold shock expression.

The current Office Action has rejected the claims for failing to meet the written description requirement. The Applicants invite the Examiner's attention to *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976), which stated that

> Two of the first paragraph requirements indicated above, i.e., the **'description of the invention' and the 'best mode' requirements, are relatively simple to comply with and thus will ordinarily demand minimal concern on the part of the Patent Office.** What is of maximum concern in any analysis of whether a particular claim is supported by the disclosure in an application is whether the disclosure contains sufficient teaching regarding the subject matter of the claims so as to enable one skilled in the pertinent art to make and to use the claimed invention. These two requirements, "how to make" and "how to use" have sometimes been referred to in combination as the "enablement" requirement, but, in one form or another, have been the subject of extended discussion in this court of recent years. *In re Angstadt,* 190 USPQ at 217. Emphasis added.

With this requirement in mind, the Applicants respectfully submit that the written description requirement is easily met by the Applicants' thorough description of the 5'-UTR's of the cold shock genes. In particular, the Applicants have identified specific exemplary sequences,

their isolation, their role in mediation of cold shock inducible genes, their particular location, and their structure in relation to other related cold box sequences.

The 1999 Revised Interim Written Description Guidelines acknowledged, that "At this time the Federal Circuit has not indicated that reduction to practice is necessary for conception or written description of a biotechnological invention." (Preamble to 1999 Revised Interim Written Description Guidelines). One of skill in the art will readily envisage the products claimed from the Applicants' process. Given the vast knowledge of the *E. coli* genome (it has been fully sequenced), the description of over 50 homologous *cspA* proteins (See Applicants' Specification at page 2-3), the well-characterized *cspA* "like proteins" and the detailed description and examples throughout the Applicants' Specification, it is redundant and not required under §112 to have the Applicants repeat the examples as set out in the Specification for all 5'-UTRs. Given the vast knowledge of cold shock genes, one skilled in the art could readily determine the cold shock's, 5'UTR role in cold shock mediation.

The Applicants respectfully submit that not all 5'-UTRs, which mediate translation, need to be disclosed to satisfy the written description requirement. Federal courts have clearly stated that possession of the claimed invention can be demonstrated through illustrative examples that describe the claimed invention. Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid for lack of written description. **"It is not a function of the claims to specifically exclude possible inoperative substances."** *Horton v. Stevens*, 7 USPQ2d 1245, 1247 (Bd.Pat.App.&Int.1988); *In re Dinh-Nguyen*, 492 F.2d 856, 858-59, 181 USPQ 46, 48 (CCPA 1974) (emphasis omitted); *In re Geerdes*, 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974); *In re Anderson*, 471 F.2d 1237, 1242, 176 USPQ 331, 334-35 (CCPA 1973).

Furthermore, it is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt,* 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976); *In re Vaeck,* 20 USPQ2d 1438 (CAFC 1991). It is well established that a patent applicant is entitled to claim the invention generically, when the applicant describes it sufficiently to meet the requirements of §112. See *Utter v. Hiraga,* 845 F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. §112, first paragraph, contain a written description of a broadly claimed invention without describing all species that the claim encompasses."); *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970).

In view of the foregoing, withdraw of the rejection of Claims 1, 3, 6-9, 11-13 and 16-57 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims Rejection Under 35 U.S.C. §102

Claims 1, 3, 5-15 and 57 stand rejected under 35 U.S.C. 102(b) as being anticipated by Goldstein et al.

Applicants respectfully submit that Claim 1 refers to a cold shock inducible gene whose expression is regulated by the 5'-UTR of the cold shock gene. In sharp contrast, Goldstein et al. refers to the *cspA* gene and its promoter, which aids in the regulation of **transcription.** As can be seen on page 5, line 14-17, "the 5'-UTR plays a major role in **translation** efficiency of the cspA mRNA." As is well understood by those skilled in the art, expression of a gene is vastly different from transcription of a gene. Further, one skilled in the art will readily recognize that promoters are involved in transcription of DNA into mRNA, which may or may not be expressed as a protein. Therefore, once RNA polymerase has transcribed DNA into mRNA, the mRNA that correlates to the promoter may or may not serve to mediate the expression of the mRNA.

A promoter is a region of DNA to which RNA polymerase binds to initiate transcription. In contrast, the 5'untranslated region (5'-UTR) is a sequence of nucleotides that extends from the 5' end of a mRNA to the 5' end of the first protein-coding region. (Copy definitions enclosed). The Applicants have discovered the particular role of the 5'-UTR in cold shock expression through a series of deletion mutations and hyper-expression experiments, which elucidated that the 5'-UTR mediates the expression of cold shock inducible genes. Essentially the 5'-UTR is a region 5' of the Translational Initiation Regions (TIRs) of mRNA that flags the correct first codon for the ribosome. As is well known, translation of a gene may be inhibited even after the mRNA has been transcribed from DNA (e.g. transcriptional and postransciptional regulation). In fact, the Court of Appeals recognized that "**Protein production involves two distinct processes--transcription and translation**. Transcription refers to the process by which a strand of messenger RNA ("mRNA") is created by the expression of a gene. Translation refers to the process by which a corresponding protein (i.e., a sequence of amino acids) is created from the mRNA." *Sibia Neurosciences Inc. v. Cadus Pharmaceutical Corp.*, 55 USPQ2d 1927, 1928 (CA FC 2000) [Emphasis added]. Applicants respectfully submit that the claims clearly illustrate that the 5'-UTR mediates the expression of a cold shock gene, whose role in expression of mRNA had not been elucidated until the Applicants' discovery.

Claims 1,3, 5-6, and 57 have been rejected under 35 U.S.C. 102(b) as being anticipated by Oppenheim et al. (U.S. Patent No. 5,726,039).

Oppenheim et al. in describes the expression of lacZ, in terms of enzyme activities and mRNA level, under the control of various *cspA* promoters, at 37°C. and 15°C. (Oppenheim et al., Fig. 19). Nowhere in Oppenheim et al., is there a description as to the role of the 5'-UTR in cold shock gene expression. Oppenheim et al. teaches the role of *cspA* promoters, not the role of

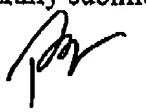
the 5'-UTR. The Office Action asserts that "a sequence of 449 nucleotides before the start codon undoubtedly comprises 5'-UTR sequence." The Applicants respectfully submit that the promoter comprises a region of DNA to which RNA polymerase binds before initiating the transcription of the DNA (e.g. a gene) into mRNA. The promoter is located upstream of the start site of transcription (e.g. the coding strand), which is the actual site of mRNA synthesis. Hence, it is respectfully submitted that the promoter region is not transcribed into mRNA, and therefore not inherently a part of the transcription product (mRNA). In sharp contrast, the Applicants claimed nucleic acid molecule which comprises a portion of the 5' UTR, which mediates **expression** of a cold shock gene. The Applicants respectfully submit that the 5'-UTR comprises a portion of the mRNA, which is upstream of the Translation Initiation Region (TIR). As a result, it is respectfully submitted that the promoter described in Oppenheim, would not necessarily comprise the Applicants' 5'-UTR sequence.

Furthermore, the Applicant's respectfully submit that the assertion that "a sequence of 449 nucleotides before the start codon undoubtedly comprises 5'-UTR sequence.", is analogous to assuming that simply because the human genome has been successfully mapped, that the **role** of all of the genetic elements (promoters, initiation sites, introns, exons, cis acting sites, terminators, etc...) and their interrelationship would "undoubtedly" be well characterized. Applicants respectfully submit that the aforementioned assertion erroneously assumes that the role of the 5'-UTR in gene expression is characterized because it may be present in the mRNA transcribed from the *cspA* promoter. However, a careful study of Oppenheim et al. reveals that it does not disclose the role of the 5'-UTR in the expression of cold shock genes. In contrast, the Applicants have claimed the role of the 5'-UTR in the mediation of the expression cold shock genes. Oppenheim et al., disclose the effect of the promoter, not the role of the 5'-UTR as it

relates to such things as translation efficiency and the enhancement and/or repression of cold shock gene expression. In view of the foregoing, Applicants respectfully request withdraw of the rejection of Claims 1, 3, 5-6, and 57 as anticipated by Oppenheim et al.

In light of the foregoing, Applicants respectfully submit that the specification and claims as amended are now in condition for allowance, which is respectfully requested.

Respectfully submitted,



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SECOND EDITION

Molecular Genetics *of* Bacteria

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Cover photograph (courtesy of Richard Losick and Masaya Fujita, Department of Molecular and Cellular Biology, Harvard University) illustrates the cellular localization of a Bacillus subtilis *sporulation-specific transcription factor,* σ^E*, as visualized with protein fusions to the "green fluorescent protein." Pro-*σ^E *first localizes to the septal and cytoplasmic membranes of sporulating cells at the stage of polar septation as shown in the cells on the right side of the insert. To the left, the mature* σ^E *is present in the cytoplasm in the large chamber of the sporangium, where it directs mother-cell-specific transcription.*

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hybridize to the sequence and allow it to be identified from among many other sequences.

Prokaryotes. Organisms whose cells do not contain a nuclear membrane and visible nucleus or many of the other organelles characteristic of the cells of higher organisms. They include the eubacteria and archaea.

Promiscuous plasmid. A self-transmissible plasmid that can transfer itself into many types of bacteria, some of which are only distantly related to each other.

Promoter. A region on DNA to which RNA polymerase binds to initiate transcription.

Prophage. The state of phage DNA in a lysogen in which the phage DNA is integrated into the chromosome of the bacterium or replicates as a plasmid.

Protein disulfide isomerase. An enzyme that catalyzes the oxidation of the sulfhydryl groups of cysteines in polypeptides, cross-linking the cysteines to each other.

Protein export. The transport of proteins into or through the cellular membranes.

Protein secretion. The transport of proteins through the cellular membranes.

Proteomics. The large-scale characterization of all the proteins of an organism.

Pseudoknot. An RNA tertiary structure with interlocking loops held together by regions of hyrogen bonding between the bases.

Purine. A base in DNA and RNA with two ring structures.

Pyrimidine. A base in DNA and RNA with only one ring.

Pyrimidine dimer. A type of DNA damage in which two adjacent pyrimidines are covalently joined by chemical bonds.

Quaternary structure. The complete three-dimensional structure of a protein including all the polypeptide chains making up the protein and how they are wrapped around each other.

R-loop. A three stranded structure formed by the invasion of a double-stranded DNA by an RNA, displacing one of the strands of the double-stranded DNA.

Random gene fusions. A technique in which transposon mutagenesis is used to fuse reporter genes to different regions in the chromosome. A transposon containing a reporter gene hops randomly into the chromosome, resulting in various transposon insertion mutants that have the reporter gene on the transposon fused either transcriptionally or translationally to different genes to different regions within each gene.

Random-mutation hypothesis. A hypothesis expla ing the adaptation of organisms to their environment states that mutations occur randomly, free of influe from their consequences, but that mutant organis preferentially survive and reproduce themselves if mutations inadvertently confer advantages under the cumstances.

RC plasmid. *See* Rolling-circle plasmid.

Reading frame. Any sequence of nucleotides in RI or DNA read three at a time in succession, as dur translation of an mRNA.

Rec⁻ (recombination-deficient) mutant. A mutant which DNA shows a reduced capacity for recombinatic

Recessive. A mutation or other genetic marker t does not exert its phenotype in an organism that diploid for the region because it also contains the co sponding region from the wild-type organism.

Recessive mutation. Referring to complementat tests, a mutation that does not exhibit its phenotype the presence of a wild-type copy of the same region DNA.

Recipient. In a genetic cross between two bacteria, bacterium that receives DNA from another bacterium

Recipient allele. The sequence of a gene or allele a occurs in the recipient bacterium.

Recipient strain. Bacteria with the genotype of th that were used as recipients in a genetic cross.

Reciprocal cross. A genetic cross in which the alleles the donor and recipient strain are reversed relative to earlier cross. An example would be a transduction which the phage were grown on the strain that had alleles of what was previously the recipient strain a used to transduce a strain with the alleles of what v previously the donor strain.

Recombinant DNA. A DNA molecule derived from sequences of two different DNAs joined to each othe a test tube.

Recombinant type. In a genetic cross, progeny that genetically unlike either parent in the cross because tl have DNA sequences that are the result of recombi tion between the parental DNAs.

Recombinase. An enzyme that specifically recogni two sequences in DNA and breaks and rejoins strands to cause a crossover within the sequences.

using an antibiotic that kills growing but not stationary-phase cells.

Epistasis. A type of interaction in which a mutation at one locus can affect the phenotype of a different locus.

Escape synthesis. Induction of transcription of an operon as a result of titration of its repressor owing to an increase in the number of operators to which the repressor binds.

Essential genes. Genes whose products are required for maintenance and/or growth of the cell under all conditions.

Eubacteria. "True" bacteria. A member of the kingdom of organisms characterized by a relatively simple cell structure free of many cellular organelles, the presence of 16S and 23S rRNAs, and usually a four-component core RNA polymerase, among other features.

Eukaryotes. Members of the kingdom of organisms whose cells contain a nucleus surrounded by nuclear membrane and many other cellular organelles, including a Golgi apparatus and an endoplasmic reticulum. Have 18S and 28S rRNAs.

Exonuclease. An enzyme which removes nucleotides one at a time from the end of a polynucleotide.

Exported proteins. Proteins which leave the cytoplasm after they are made and end up in a membrane, in the periplasmic space, or outside the cell.

Expression vector. A cloning vector in which a cloned gene can be transcribed and sometimes also translated from a vector promoter and translation initiation region, respectively.

Extracellular protein. A protein that is excreted from cells after it is made.

Extragenic. Involving a different gene.

Extragenic suppressor. A suppressor mutation that is in a gene different from the gene encoding the mutation that it suppresses.

Factor-dependent transcription termination site. A sequence on DNA that causes transcription termination only in the presence of a particular protein such as the Rho protein of *E. coli*.

Factor-independent transcription termination site. A sequence in DNA that causes transcription termination by RNA polymerase alone, in the absence of other proteins. In bacteria, characterized by a GC-rich region with an inverted repeat followed by a string of A's on the template strand.

Feedback inhibition. Inhibition of the synthesis of the product of a pathway that results from binding of the end product of the pathway to the first enzyme of the pathway, thereby inhibiting activity of the enzyme.

Filamentous phage. A phage with a long, floppy appearance. The nucleic acid genome of these phages is merely coated with protein, making the phage as long as the genome and giving the floppy appearance. In contrast, the nucleic acids of most phages are encapsulated in a rigid, almost spherical, icosahedral head.

Filter mating. Procedure in which two bacteria are trapped on a filter to hold them in juxtaposition so that conjugation can occur.

5′ end. The end of a nucleic acid strand (DNA or RNA) in which the 5′ carbon of the ribose sugar is not attached through a phosphate to another nucleotide.

5′ exonuclease. A deoxyribonuclease (DNase) that degrades DNA starting with a free 5′ end.

5′ overhang. A short, single-stranded 5′ end on an otherwise double-stranded DNA molecule.

5′ phosphate end. In a polynucleotide, a 5′ end that has a phosphate attached to the 5′ carbon of the ribose sugar of the last nucleotide.

5′ untranslated region. The sequence of nucle tides that extends from the 5′ end of an mRNA to the 5′ end of the first protein-coding region.

Flanking sequences. The sequences that lie on either side of a gene or other DNA element.

Formylmethionyl-tRNA$_f^{Met}$. The special tRNA in prokaryotes that is activated by formylmethionine and is used to inititate translation at prokaryotic translation initiation regions (TIRs). It binds to translation initiation factor IF2 and responds to the initiator codons AUG and GUG and, more rarely, to other codons in a TIR.

Four-hitter. A type II DNA restriction endonuclease that recognizes and cuts at a 4-bp sequence in DNA.

4.5S RNA. The RNA component of the signal recognition particle (SRP) of bacteria.

Frameshift mutation. Any mutation that adds or removes one or more (but not a multiple of 3) base pairs from DNA, whether or not it occurs in the coding region for a protein.

Functional domain. The region of a polypeptide chain that performs a particular function in the protein.

Functional genomics. The use of techniques such as reverse genetics, microarrays, and proteomics to study the functions of a sequenced genome.